THE ALKALOIDS OF THE GENUS SENECIO

BEING

A THESIS

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BY

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C O N T E N T S.

THE ALKALOIDS OF THE GENUS SENECIO.

Part I.

REVIEW OF THE LITERATURE.

Introduction.

The genus Senecio belonging to the natural order Compositae is the largest genus of flowering plants, comprising over 1200 species, which are widely distributed throughout the world.

It is also the chief genus of the order to show well defined alkaloids in appreciable quantities.

Various species of Senecio have been used domestically in the treatment of ailments for a considerable time.

In James' Pharmacopoeia Universalis or Universal Dispensatory (London 1747) , Erigerum, Senecio vulgaris Park., Groundsel or Simson is described as used and said to be beneficial in the cholera, jaundice, intemperature of the blood and sciatic pains. Externally it was applied to remove inflammation of wounds. Jacobaea vulgaris major Park. Ragwort or Seggrum has the same virtues as Groundsel.

It cures all wounds and inflammations and is an excellent gargle against quinsy and inflammation of the tonsils.

In Gray's Supplement to the Pharmacopoeia (London 1848) the following species are recorded;-

Senecio Cacaliaster Lamb. South of France. Used in coughs; the juice allays tickling in the throat.

Senecio Doria Linn. Doria's Woundwort. South of France. Leaves used externally and internally in wounds and malignant ulcers.

Senecio Doronicum Linn. Alpine Groundsel. South of France. Infusion and steam of the infusion used in asthma.

Senecio Jacobaea Linn. Ragwort. Used in poultices for colic pains and as a gargle for sore throat.

Senecio Sarracenicus Jacq. Broad -leaved Ragwort. Sarracen's Woundwort. Leaves used externally and internally in wounds and malignant ulcers.

Senecio tomentosus Michx. North America. Yellow bark powerfully anthelmintic.

Senecio vulgaris Linn. Common Groundsel. Weak infusions a common purge. Strong infusions of juice as an emetic. Leaves externally suppurative. A popular but useless vermifuge.

The following references to additional species are from Dragendorff's Heilpflanzen, 1898:-

Senecio Fuchsii Gmel., Senecio nemorensis L. and Senecio undulatus Thumb. Middle Europe. Used against catarrh.

Senecio Canicida Moc. and Senecio vulneraria DC. Mexico. Supposed to be poisonous to dogs. Herb and root contain an irritating tetanic poison.

Senecio tolutanus DC. Mexico. Contains a tetanus producing alkaloid Toxisenecine.

Senecio Balsamitae and Senecio obovatus Muhlb. North America. Employed as haemostatics for capillary haemorrhage.

Senecio nigrescens Hook. Chili. Intermittent.

Senecio Ambavilla Pers. Bourbon. Recommended as an antisyphilitic.

Senecio Cineraria DC. South America. Juice prescribed for eye ailments and as an emmenagogue.

Senecio acanthifolius Kost. Egypt. Recommended for kidney and urinary calculus.

Senecio crucaefolius L. and Senecio paludosus L. Alkaloids have been detected. In South Russia used as salves.

Senecio viscosus L. and Senecio sylvaticus L. Poor in alkaloid.

Senecio Haworthii. Cape. Herb used for chest diseases.

Senecio succulentus DC. And Senecio ficoides Sch. Cape. Leaves and stalks edible.

Senecio Kleinia Less. India. Employed against leprosy affections.

Senecio pendulus DC. Arabia. Juice instilled against ear pains.

Senecio odorus Sch. Employed as a diuretic and as a fumigating disinfectant.

Senecio sagittatus Sch. Serves as a popular remedy.

Senecio antieuphorbius Sch. Abyssinia. South Africa. Mucilaginous. Demulcent. Antidote against poisonous Euphorbias.

In The Medicinal and Poisonous Plants of South Africa, Watt and Breyer-Brandwijk, some twenty species of Senecio are described as being used by the natives of South Africa for a variety of ailments.

The species specially employed in medicine have been Senecio vulgaris and Senecio Jacobaea and many references to their use are recorded.

Senecio vulgaris was formerly official in the French Codex in the form of the dried leaves

but is not included in the present edition.

A fluid extract of Senecio aureus, Golden Ragwort, Life Root or Squaw Weed, indigenous to North America, while not official in the Pharmacopoeia of the United States of America, is included in the National Formulary of that country.

The extract is stated to prove efficacious in stopping capillary haemorrhage, especially in haematuria, haemophysis and menorrhagia.

Senecio vulgaris, Senecio Jacobaea, Senecio maritima and Senecio aureus still find a place in modern herbals.

The rhizomes of the Mexican species, Senecio Grayanus Henckel and Senecio cervariaefolius Sch. constitute Maturin, the plants being known as Matarique or Guerena.

They produce rise of temperature, dilations of the pupil and violent tetanic spasms.

Henckel states that they contain a glucoside resembling digitalin.

Westling in a description of Madagascar drugs states that the leaves and stems of Senecio fauyasoides, which is known as Hanidraisoa and is used against syphilis and for the intestinal disease known as "Tanbavy", contains inulin and an alkaloid

probably allied to Senecine. A non-alkaloidal crystalline substance is also present, which can be sublimed and crystallises from ethyl acetate in needles.

Pharmacological Action of the Senecio Species.

Senecio canicida Moc., a native species of Mexico, known as "Yerba de los perros", and used, as its name implies, to poison dogs, was investigated by Debierre in 1888.

The active principle, stated to be more abundant in the roots than in the leaves, was not isolated.

Three stages occur in the poisoning arising from its use, viz; a period of excitation, then one of rest and lastly a spasm. The temperature rises and remains high until the animal dies, death taking place from paralysis of respiration.

Although it causes tetanic symptoms like those of strychnine, it differs from that alkaloid in lowering reflex excitability.

The various species in this country are generally regarded as harmless, the chief of them being Senecio Jacobaea, Common Ragwort, and Senecio vulgaris, Common Groundsel.

In Nova Scotia, New Zealand and South Africa, however, certain species give rise to a peculiar liver disease in cattle and horses, which is known as Picton, Winton, Molteno and "dunsiekte" disease

in these countries.

In Norway the cattle die of a disease known as "Sirasyke", which has the characteristic symptoms of Senecio poisoning, and is attributed to the eating of Senecio Jacobaea, a species which is abundant in that country.

The species which causes the disease in Canada and New Zealand is apparently identical botanically with Senecio Jacobaea, Common Ragwort of this country.

In South Africa the Molteno cattle sickness or straining disease, and "dunsiekte", stomach staggers, grass staggers or Molteno disease in horses, have been ascribed to the eating of various species of Senecios.

According to Chase, affected cattle become "unthrifty", but do not show serious symptoms for some time. A few days before death diarrhoea develops, but it may not be marked. It is accompanied by straining which often increases in intensity and frequency.

Finally the animal becomes unconscious and dies in from two to four days from the onset of diarrhoea and other symptoms.

Post mortem examination reveals cirrhosis of the liver.

The earliest symptoms of "dunsiekte", according to Verney, are yawning and gaping, and affected horses tend to remain solitary and lose in condition. A staggering gait develops and near the end the animal has great difficulty in keeping its balance.

Post-mortem examination shows the typical cirrhotic changes in the liver.

Steyn records that the administration of Senecio isatideus DC., Dan's Cabbage (one of the species examined in this thesis) produces fatal poisoning in sheep, the plant apparently being more toxic in the flowering stage than in the late seeding stage.

The symptoms are respiratory and cardiac acceleration, listlessness and weakness, and slight jaundice.

Post-mortem examination is characteristic of Senecio poisoning.

Senecio venosus Harv. (another species examined in this thesis) is not acutely toxic to the sheep or rabbit.

The most important work on the pharmacological action of the Senecio species was carried out by Cushny in 1911.

The alkaloids of Senecio latifolius (described later) were examined and were found markedly toxic.

The symptoms are described as being of two kinds, acute and sub-acute. The acute symptoms appear first and apparent recovery takes place. Then after two or three days the sub-acute symptoms appear and generally terminate in death in 48 hours.

The two alkaloids from Senecio latifolius induced the same symptoms and the same changes and seemed to be equally toxic.

The whole of the symptoms appeared to arise from two different effects, one of them being an action on the central nervous system resembling that seen in many convulsive poisons, but the action was only induced by large doses.

On the other hand,when smaller doses were given, the dominating effect was haemorrhage, which occurred in almost any organ but which was constant in the liver and was almost invariably present in the stomach and bowel, and the destruction of the liver cells appeared to be the starting point for cirrhosis.

The liver of some of the animals was found

to present the appearance of chronic cirrhosis and in others there was marked venous congestion of that organ.

The results obtained from Senecio latifolius suggested to the same author an examination of Senecio Jacobaea of this country.

Enquiries in various parts of this country indicated that poisoning with this plant was unknown.

Extracts of large doses gave no toxic symptoms and although the same species grown in Canada had been shown to induce the characteristic cirrhosis, an extract of the plant grown in this country also proved inactive.

It would appear that the plants from which the latter extract was prepared had either been collected at the wrong season or the alkaloids had undergone changes in the course of preparation.

Senecio sylvaticus. collected in Yorkshire in August. proved equally inactive, while Senecio vulgaris, Common Groundsel, collected in England, and prepared in the same way proved poisonous and animals died from symptoms resembling those arising from Senecifoline but with marked diarrhoea.

Subsequent experiments by Cushny with Senecio

Jacobaea gave fatal toxic results, both with Canadian and British plants.

Senecio sylvaticus and Senecio vulgaris were also proved poisonous.

In the Year Book of Pharmacy, 1921, it is stated that Senecio poisoning is not common in Great Britain, but an outbreak occurred during the war, which was probably due to the abnormally large amount of Ragwort in the hay used during that period.

It is also stated that in English pastures Ragwort is generally avoided by grazing stock, so that the plants stand up conspicuously even in close cropped fields.

I have observed that Senecio Jacobaea is not found in pastures where sheep are grazing, but it is frequently very conspicuous and abundant in fields where cattle alone are grazing.

It would appear that sheep eat the young plants and are more resistant to the effects of Senecio poison.

Willmott and Robertson in 1920 reported attacks of illness, many of them fatal, which occurred in some eighty cases in South Africa, among patients of the poorer classes whose staple

food was bread.

These were ultimately traced to flour ground from wheat grown in the George and Mossel Bay districts, which was contaminated with the seeds of Senecio ilicifolius and Senecio Burchelli.

The symptoms were more or less gastric disturbance, enlargement of the liver and dropsy. The seeds administered to animals occasioned similar symptoms and gave rise to the same post-mortem appearance of the organs as was found in the human cases of flour poisoning.

Senecio vulgaris and Senecio Jacobaea were examined in 1926 by Hamet and Vignes, who found that the plants were toxic in large doses, causing excitation of the longitudinal intestinal fibres, paralysing the anal and vesical sphincters, causing intestinal and pulmonary dilation, lessening the amplitude of uterine contraction and causing mydriasis.

They state that in therapeutic doses preparations of Senecio may prove useful in the treatment of menstrual disorders and quote a case where Senecio proved effective after Ergot had failed.

The toxicity of Senecio Riddelli, a species found in North America, was investigated by Bukey

and Cunningham in 1933 and observations on horses are recorded.

I learn from private information that the species is now the subject of a chemical investigation by one of the above named workers.

The alkaloid Retrorsine from Senecio Retrorsus and a liquid extract from a species of Senecio were examined by Davidson in 1934 for their action on rat's liver and it was found that profound changes took place.

First there was a notable endothelial cell proliferation in the branches of the hepatic vein with consequent rupture and haemorrhage beginning in the centre of the lobules.

Similar changes, though of a lesser degree, may also be present in the pulmonary and cerebral vessels.

Neurosis of the hepatic cells of the central and mid zones follows and finally there is a replacement fibrosis with regeneration of liver cells and bile ducts, provided the animal lives for a sufficient length of time, the final effect being that of interstitial hepatis or cirrhosis.

The primary effect of the alkaloid appears to be vascular.

The Chemistry of the Senecio Species.

The earliest workers on the alkaloids of the Senecio species were Grandval and Lajoux, who, in 1895, described two alkaloids, one crystalline, which was named Senecionine, and the other amorphous, named Senecine, obtained from Senecio vulgaris.

The formula of Senecionine was found to be $C_{18}H_{25}O_6N$, but the amount of Senecine isolated did not permit of the formula being determined.

They were led to the examination of this species on account of an article which appeared in the British Medical Journal, where Senecio, no species stated, was described as being used in certain parts of England for the treatment of amenorrhoea.

Senecine was found to differ from Senecionine in being soluble in ether and in forming an acid tartrate which was little soluble in cold water, and in possessing a bitter taste.

Certain colour reactions which distinguish Senecine from Senecionine are also described.

No crystalline salts of Senecionine were obtained.

The same authors also studied Senecio Jacobaea and isolated two alkaloids, one soluble and the other

insoluble in ether but soluble in chloroform.

The physical characters and reactions are described as identical with those of Senecionine and Senecine, which were obtained from Senecio vulgaris.

Lutz found in several other species of Senecio the two alkaloids, Senecionine and Senecine, which were detected in minutes quantities in Senecio vulgaris by Grandval and Lajoux.

He states that in all cases they occur in the underground parts only to the exclusion of the aerial organs, and that they were found in largest quantities in Senecio erucifolius and Senecio palustris, and to a smaller extent in Senecio Jacobaea and Senecio cineraria.

The tissues in which they are chiefly present are in the pith, the liber and the cortical parenchyma.

Senecio latifolius DC., a native species of South Africa, was examined by Watt in 1909, and he isolated two crystalline alkaloids, which he named Senecifoline, $C_{18}H_{27}O_8N$ and Senecifolidine, $C_{18}H_{25}O_7N$.

The crude alkaloidal residue from the extraction was separated into the two alkaloids by neutralising with dilute nitric acid and evaporating

the solution in vacuo, when Senecifoline Nitrate crystallised out, leaving Senecifolidine Nitrate in solution.

Senecifoline was hydrolysed with an alcoholic solution of sodium hydroxide and separated into a basic part called Senecifolinine, $C_8H_{11}O_2N$, and an acidic fragment called Senecifolic Acid, $C_{10}H_{16}O_6$, which was considered a monocyclic dihydroxycarboxylic acid.

The rhizomes of Ligularia tussilaginea, (Senecio Kaempferi) a Japanese evergreen plant, were examined by Shimoyama and were found to contain an acid crystalline principle of the formula $C_5H_8O_2$, to which the leaves are said to owe their property of imparting a red colour to the skin.

The acid principle was further investigated by Asahina in 1913, who named it Senecionic Acid and found it identical with ββ-dimethylacrylic acid.

Its calcium salt has the formula $(C_4H_7CO_2)_2Ca$.

The plant chemistry of Senecio Jacobaea was the subject of an investigation by Keegan in 1915, who found that a benzene extract of the leaves yielded carotin; an alcoholic extract a flavone but no alkaloid; and the aqueous extract a little caffetannin, much mucilage and a bitter principle.

The roots examined in September gave a little

caffetannin, much carbohydrate yielding saccharose and pentose, but no starch, no glucose and no alkaloid.

Müller in 1921 gave a very comprehensive account of the literature dealing with the Senecio species.

He also investigated two species, Senecio Fuchsii and Senecio sylvaticus, and isolated from the former an alkaloid which he named Fuchsi-senecionine, $C_{12}H_{21}O_3N$, and another base $C_9H_{13}O_2N$, and from the latter an alkaloid which he called Silvasenecine, $C_{12}H_{21}O_4N$.

The alkaloids were isolated from the crude residue as the aurichlorides, from which the hydrochlorides were obtained, and the method was found most useful in my investigation of Senecio saracenicus, when at first I failed to crystallise the base from the usual solvents.

The crude base of Senecio Fuchsii was found to be soluble in alcohol, easily soluble in chloroform, practically insoluble in ether and soluble for the greater part in water with a strong alkaline reaction. It is stated to have a reducing action similar to the alkaloids of Senecio vulgaris.

The crude base of Senecio sylvaticus was not so readily soluble in chloroform, but had similar properties to the base of Senecio Fuchsii.

In 1931 Manske obtained a new alkaloid from Senecio retrorsus DC., from material of South African origin, which he named Retrorsine, and to which he assigned the formula $C_{18}H_{25}O_6N$. This was confirmed by analysis of the hydrolytic products, Retrorsine on hydrolysis yielding the base Retronecine, $C_8H_{13}O_2N$, separated as the hydrochloride, and an acid, $C_{10}H_{16}O_6$, called Retronecic Acid.

Senecio retrorsus yielded to chloroform extraction another substance which crystallised with great facility in large colourless hexagonal plates. The analysis indicated the formula $C_{12}H_{16}O_7$, but its properties have not been investigated.

The same author also examined Senecio Jacobaea in a similar manner and isolated an alkaloid which he called Jacobine with an empirical formula $C_{18}H_{23}O_5N$, which was partly confirmed by analysis of the hydrolytic products.

Jacobine on hydrolysis yielded a "necine" which was found identical with Retronecine $C_8H_{13}O_2N$, and a "necic""acid named Jaconecic Acid, the

formula of which $C_{10}H_{16}O_6$, is given with reserve.

A second substance was also obtained from this species as a phenylhydrazone for which the formula $C_7H_6O_2$:N.NH.$C_6H_5$is given.

An examination of Senecio aureus yielded a small amount of a pale yellow resin which could not be crystallised, but which was alkaloidal in properties.

Senecio aureus, indigenous to North America and known as Golden Senecio, Ragwort, Squaw Weed or Life Root was also investigated by Kelly and Lynn in 1931, who reported the extractive value of various solvents.

They separated a volatile oil up to 0.2% and found that it contained 1.22% of sulphur.

From their examination they concluded that several alkaloids are contained in Senecio aureus, some so weakly basic that they cannot be extracted from acid solution. They also found that part or all the bases are volatile in steam, but no alkaloid was isolated.

Retrorsine, the alkaloid of Senecio retrorsus was further investigated by Barger, Seshadri, Watt and Yabuta, who obtained the alkaloid from authentic material, indentified by botanists.

They call attention to the fact that botanists have recently divided Senecio latifolius into several species, and suggest that the material previously examined by Watt was not homogenous, and that the source of the alkaloids Senecifoline and Senecifolidine is uncertain.

It is also suggested that the hydrolytic product Senecifolinine is identical with Retronecine, though the other fission product, Senecifolic Acid, differs from Retronecic Acid, with which it is isomeric.

A number of derivatives of Retrorsine are described and also a convenient method for the hydrolysis of the alkaloid.

Retrorsine was reduced catalytically and took up two molecules of hydrogen.

The reduced alkaloid was obtained as a white amorphous powder, which was extremely soluble in water, and could not be crystallised. It yielded on hydrolysis a new base Retronecanol, $C_8H_{15}ON$.

Senecio platyphyllus DC., one of about fifty species occurring in the U.S.S.R., was recently investigated by Orechoff, who isolated two crystalline alkaloids from the dried roots of the plant, which he named Platyphylline, $C_{17}H_{25}O_5N$, and

Seneciphylline, $C_{17}H_{23}O_5N$.

The two alkaloids were separated by fractional crystallisation from absolute alcohol, Seneciphylline being the least soluble base in that solvent.

The hydrolysis of Platyphylline was carried out and yielded a base, Platynecine, $C_7H_{11}O_2N$, isolated as the aurichloride, and a monobasic acid, named Platynecic Acid, $C_{10}H_{14}O_4$.

A number of derivatives of both alkaloids are described.

The following table shows the alkaloids previously isolated from Senecio species.

Species.	Alkaloid.	% yield of dried wt.	Author.
S. vulgaris.	Senecionine.	0.006 to 0.048	Grandval & Lajoux.
"	Senecine.		
S. latifolius.	Senecifoline.	1.2 to 0.49	Watt.
"	Senecifolidine.		Watt.
S. Fuchsii.	Fuchsisenecionine.	-	Müller.
S. sylvaticus.	Silvasenecine.	-	Müller.
S. retrorsus.	Retrorsine.	1.3	Manske.
S. Jacobaea.	Jacobine.	0.04	Manske.
S. platyphyllus.	Platyphylline.	1.05	Orechoff.
"	Seneciphylline.		Orechoff.

The chemical papers so far published indicate two types of Senecio alkaloids;-

Group I. Alkaloids very soluble in chloroform and containing about 18 carbon atoms.

Group II. Alkaloids soluble in water and very soluble in chloroform and containing about 12 carbon atoms.

In the present investigation some eleven more species have been examined and examples of both types of alkaloids have been found.

At first I thought that each species contained only one specific alkaloid as no obvious mixtures were obtained, and this seems to have been an assumption made by Manske, who suggested that in order to simplify the nomenclature, the alkaloid should be named after the species, and that the generic name "necine" be applied to the basic hydrolytic product and the name "necic" acid for the acidic fragment, e.g. the whole alkaloid of Senecio retrorsus he named Retrorsine, and the hydrolytic products, Retronecine and Retronecic acid.

As far as possible this plan has been adopted, but in the course of the work some species yielded more than one alkaloid and other names have been applied.

The following table shows the alkaloids isolated in this investigation of the following Senecio species.

New alkaloids are underlined.

Species.	Alkaloid.	Formula.
<u>South African.</u>		
S. retrorsus.	Retrorsine.	$C_{18}H_{25}O_6N$.
S. glaberrimus.	"	"
S. venosus.	"	"
S. isatideus.	<u>Isatidine.</u>	$C_{18}H_{25}O_7N$.
"	Retrorsine.	$C_{18}H_{25}O_6N$.
<u>British.</u>		
S. vulgaris.	Senecionine.	$C_{18}H_{25}O_5N$.
S. aquaticus.	"	"
S. viscosus.	"	"
S. Jacobaea.	<u>Jacocine.</u>	$C_{17}H_{23}O_5N$?
"	<u>Jacodine.</u>	$C_{18}H_{25}O_5N$.
"	<u>Jaconine.</u>	$C_{17}H_{23}O_7N$.
S. erucifolius.	<u>Erucifoliné.</u>	$C_{18}H_{27}O_5N$?
S. saracenicus.	<u>Saracebine.</u>	C_5H_9ON ?
"	<u>Saracedine.</u>	$C_8H_{13}ON$.
"	<u>Saracenine.</u>	$C_{13}H_{21}ON_3$.

SPECIES NOW INVESTIGATED.

BOTANICAL.

South African Species.

The following descriptions are taken from the Flora Capensis (Harvey & Sonder, 1864).

Senecio retrorsus DC. is given as a variety of Senecio latifolius DC., a tall plant, two feet or more in height, woolly on the crown of the root, otherwise quite glabrous; stem erect, striate, leafy, ending in a much branched corymbose panicle; lower leaves oblong or obovate, acute or acuminate, tapering to the base, entire or remotely denticulate; upper leaves cordate-eared and clasping at the base, oblong or lanceolate or linear acuminate; partial corymbs many leaved, pedicels short, nearly nude; involucre of 5 to 8 glabrous nerve scales; disc flowers 10 - 12, rays 3 - 5, achenes quite glabrous.

Senecio retrorsus appears to differ from Senecio latifolius chiefly in the size of the leaves, which are described as being 3 to 4 inches long and ¾ to 1 inch wide.

Habitat:- Uitenhage, Albany and Caffraria. Natal.

Senecio Isatideus DC. is 2 to 3 feet high, leafy for six to twelve inches below, ending in a much branched efflorescence.

It is quite glabrous except for the woolly crown of the rhizome; stem erect, leafy below, nude above ending in a corymbose panicle; lower leaves 4 to 6 inches long, 2 to 3 inches wide, oblong obovate, tapering at the base into a short winged petiole, obtuse or mucronate, callous, denticulate, mid-ribbed and penni-nerved; upper stem leaves clasping, oblong or lanceolate, much smaller.

The partial corymbs are densely many headed with short pedicels; heads 5 - flowered, discoid; involucre nearly nude at the base, funnel shaped of 5 oblong, obtuse or sub-acute glabrous scales; achenes glabrous.

Habitat:- Cape.

Senecio glaberrimus DC. is herbaceous, about 18 inches high, quite glabrous, rigid stem, simple, slender, angular, corymbose at summit; cauline leaves sessile, distant, ovate, acute, slightly cordate and clasping at the base, 3 inches long, quite entire, penni-nerved.

Corymb slightly compound, fastigate, pedicels

nearly nude; involucre half as long as disc of 10 acute scales; disc florets 20-25, ray 4 to 5; achenes glabrous.

The above diagnosis answers equally well for Senecio bupleuroides (Flora Capensis).

Habitat:- Omsamcaba, Omtendo and Osamculo.

Senecio venosus Harv. is a tall plant with the habit of Senecio isatideus, but lower part of the stem not being available, is not fully described.

The plant is apparently tall with close placed, strongly and coarsely veiny, very rigid leaves, which are 2-3 inches long and ½ to ¾ inch wide.

Cauline leaves cordate at the base and stem clasping, lanceolate, acuminate, rigidly coriaceous, thick, ciliato-denticulate, glaucescent, conspicuously veined on both surfaces.

Partial corymbs few headed, short, heads 10-flowered, discoid; involucre nude at base, funnel shaped of 5-6 oblong, obtuse, glabrous scales; achenes glabrous.

Habitat:- Magalisberg.

British Species.

Only eleven species are described in the British Flora (Bentham & Hooker), and of that number, four, Senecio squalidus L., Senecio paludosus L., Senecio palustris L. and Senecio campestris DC. are very rare and only occur in certain localities in England.

I collected the remaining seven species which were very carefully identified.

Senecio vulgaris L. Common Groundsel is an erect, branching annual, from 6 inches to nearly a foot high; glabrous; leaves pinnatifid with ovate toothed lobes.

Flower heads in close terminal corymbs with florets all tubular.

Habitat:- It is a very common weed of cultivation throughout Europe, and is abundant in Britain.

Senecio viscosus L. Viscous or Stinking Groundsel is a coarser, harder and taller annual than Senecio vulgaris, covered all over with a viscid, strong smelling substance.

The leaves are more deeply divided, with narrower lobes, and the flower heads rather thicker

with more florets on longer peduncles, forming a loose terminal corymb.

Habitat:- It extends over a great part of Europe, and is scattered over various parts of England and Scotland.

It is often found on shale and ballast heaps, but it is a rare plant, very local and seldom abundant.

Senecio sylvaticus L. Wood or Mountain Groundsel is an annual with the foliage much like that of Senecio vulgaris but it is a taller and weaker plant, sometimes 2 feet or more in height. It is not so viscid nor so strong smelling as Senecio viscosus.

It is easily distinguished from the latter in having much smaller flower heads.

Habitat:- On banks and in waste places in somewhat shady places. It extends from Scandinavia to the Mediterranean. Found in most parts of Britain but is not generally common.

Senecio aquaticus L. Marsh Ragwort or Senecio is not always easily distinguished from Senecio Jacobaea, Common Ragwort, but apart from the

different habitat, the plant has larger and fewer flower heads and laxer branching. It is 2 to 3 feet high.

The stem and leaves have a purplish or blue tint, which is characteristic of the species, though not mentioned in Floras.

Habitat:- It is spread all over Europe and is very common in marshy ground, especially along ditches.

Senecio Jacobaea L., Common Ragwort is 2 to 4 feet high, erect, with little branching. The leaves are pinnate, with ovate, obovate, or narrow, coarsely toothed segments.

The flower heads are large, bright yellow, in a compact, terminal corymb. Florets of the ray 12 to 15.

Habitat:- All over Europe and Russian Asia.

It is very common on roadsides and in waste places in Britain.

Senecio erucifolius L. Narrow-leaved Senecio or Hoary Ragwort also resembles Senecio Jacobaea, from which it can be distinguished by its shortly creeping rootstock and by the more regularly divided and narrower segments of the leaves.

The plant is also covered with downy hairs.

Habitat:- The species is common in Central and Southern Europe, frequent in England but very rare in Scotland, only occurring in isolated patches and not plentiful.

Senecio saracenicus L. Broad-leaved Ragwort is a tall perennial plant, 3 to 6 feet in height, with large, long, sessile, broadly lanceolate leaves.

Flower heads numerous in a compact corymb.

Habitat:- It is found all over Europe, but is very local in Britain and comparatively rare in Scotland.

ISOLATION OF ALKALOIDS FROM THE ABOVE SPECIES.

Group I.

South African Species.

By far the richest in alkaloids are the species from South Africa.

The material was supplied through the co-operation of the Director General of Veterinary Services of the Union of South Africa.

From Senecio retrorsus DC. the alkaloid Retrorsine, $C_{18}H_{25}O_6N$ was obtained, and has been principally used for chemical structure.

Senecio glaberrimus DC. and Senecio venosus Harv. were examined for the first time and yielded Retrorsine in smaller amounts.

From Senecio isatideus DC. a new alkaloid was isolated, for which the name Isatidine is suggested. Analytical results are in agreement with the formula $C_{18}H_{25}O_7N$, which is confirmed by the analysis of the hydrolytic products.

On hydrolysis Isatidine yields a base, which after Manske's method of nomenclature, is called Isatinecine, $C_8H_{13}O_3N$, and an acid, Isatinecic Acid, $C_{10}H_{16}O_6$, which is isomeric with Retronecic Acid and Watt's Senecifolic Acid.

$$C_{18}H_{25}O_7N + 2H_2O = C_8H_{13}O_3N + C_{10}H_{16}O_6$$

Isatinecine gives a dibenzoyl derivative by the Schotten Baumann method, the composition of which corresponds to a Dibenzoyl-anhydro-isatinecine, $C_8H_9O_2N(C_6H_5CO)_2$.

One benzoyl group must, therefore, be on the nitrogen atom, and the pyrrolidine ring has presumably been opened, as in the case with the glyoxaline ring, when Histamine, for instance, is benzoylated.

Isatidine is available in fair quantity, and since its basic hydrolytic product, Isatinecine, appears to be Hydroxy-retronecine, it is hoped to base the constitution of Isatidine on Retrorsine.

Senecio isatideus also yielded a second alkaloid, which was identified as Retrorsine.

British Species.

The alkaloidal content of the British species is much smaller and this is indeed probably the reason why the plants have been so little investigated in the past.

The special facilities at my disposal enabled me to work up large quantities of material, and for this investigation I collected about 1400 lbs. of fresh plants.

The only British species worked at to any

extent, have been Senecio Vulgaris, from which the alkaloid Senecionine, $C_{18}H_{25}O_6N$, was obtained by Grandval and Lajoux; and Senecio Jacobaea, from which Manske isolated the alkaloid Jacobine, $C_{18}H_{25}O_5N$.

Both plants are very common so that the only difficulty is one of extraction on a large scale, which is necessary in order to get a quantity of the alkaloids.

In the other species the further difficulties of collection arise, but in this connection I was fortunate in having the assistance of another botanist, Mr. George Taylor, Cockburnspath, and from his district Senecio Jacobaea and Senecio viscosus were collected in large quantities, as well as smaller batches of Senecio aquaticus and Senecio sylvaticus.

Among the British species Senecio viscosus proved valuable in giving the maximum yield of alkaloid (0.075%) from young plants collected before flowering in early June.

It was also especially valuable in that there was no appreciable quantity of a second base so that the pure alkaloid, Senecionine, was first obtained from this species.

One might indeed be tempted to call the alkaloid Viscosine, but Senecionine, the older name, has been retained, although there is a discrepancy in the formula $C_{18}H_{25}O_6N$ suggested by Grandval and Lajoux.

The analysis of pure Senecionine corresponds to the formula $C_{18}H_{25}O_5N$ and not $C_{18}H_{25}O_6N$, and this is confirmed by the analysis of the hydrolytic products.

It is possible that the base examined by the above named workers was a hydrated form of Senecionine, $C_{18}H_{25}O_5N \cdot H_2O$.

The hydrolysis of Senecionine was not carried out by Grandval and Lajoux. The basic fragment was found to be identical with Retronecine, $C_8H_{13}O_2N$, and the new acidic fragment, $C_{10}H_{14}O_4$, is best named after Manske's plan, Visconecic Acid (alternatively Vulganecic Acid).

One molecule of water is taken up in the hydrolysis according to the following equation

$$C_{18}H_{25}O_5N + H_2O = C_8H_{13}O_2N + C_{10}H_{14}O_4$$

Visconecic Acid, $C_{10}H_{14}O_4$, is a monobasic acid, isomeric with Orechoff's Platynecic Acid, and although the melting point and the optical rotation are somewhat near those of the latter acid

it appears to differ from Platynecic Acid in being very soluble in water.

In Senecio vulgaris a second base Senecine, with bitter taste, accompanied the main alkaloid, Senecionine, as already indicated by Grandval and Lajoux.

I have failed to isolate Senecine, but its presence or that of some other base made it at first difficult for me to obtain pure Senecionine, which showed itself in particular by my inability to crystallise the acid on hydrolysis of the alkaloid from the first batch of Senecio vulgaris, but which was afterwards first obtained crystalline as Visconecic Acid from pure Senecionine from Senecio viscosus.

The second batch of Senecio vulgaris, which was collected in September and October, yielded pure Senecionine. The alkaloid now showed the same melting point and approximately the same optical rotation as pure Senecionine from Senecio viscosus.

Further the alkaloid on hydrolysis yielded the pure Visconecic Acid in a crystalline form.

The yield of alkaloid was found to have decreased considerably, confirming the observations of Grandval and Lajoux, but it would also appear that

there is a change in the proportions of the two bases as the season advances.

Another supply of Senecio vulgaris has recently (April 1935) been collected, and it is hopedto investigate this species further with a view to determining the seasonable variations of the alkaloidal content.

The difficulties of obtaining a really pure alkaloid, encountered to some extent with Senecio vulgaris, were exceeded in the case of Senecio Jacobaea.

Although the melting point of the alkaloid was fairly constant, there was considerable variation in the optical rotations, not only in the alkaloids from the two batches, but also in the various fractions obtained from the recrystallisation of the alkaloid from the second batch of plants.

In general it is essential to purify the various alkaloids until the optical rotation is constant. Manske in his examination of Jacobine from Senecio Jacobaea neglected to do this.

The melting point is of no use, and the solubility and volatility in a high vacuum of little assistance in determining the purity of the Senecio

alkaloids.

The difficulties are caused by the presence of two very similar alkaloids, which were ultimately separated in a fairly pure state by the careful fractional crystallisation of the nitrates from absolute alcohol.

From the least soluble nitrate a base was obtained to which the name Jacocine has been applied and from the more soluble nitrate a base now termed Jacodine.

It was then found that the bases could be separated by taking advantage of their different solubilities in ethyl acetate. Fortunately the base from the more soluble nitrate is itself the less soluble in ethyl acetate, so that the bases regenerated from the nitrates in the first instance were thus obtained in a pure condition.

Analytical figures based on the analysis of the nitrate are in agreement with the formula $C_{17}H_{23}O_5N$, but the analysis of the base recently determined do not fit this formula but are moderately in agreement with the formula $C_{18}H_{23}O_6N$.

Jacocine on hydrolysis yielded a base identified as Retronecine, $C_8H_{13}O_2N$, but the acidic fragment was obtained as a syrup which became partly

crystalline on long standing in a vacuous desiccator. So far it has not been analysed, but a specimen of an acid previously obtained from the hydrolysis of the mixed alkaloids, on analysis gave results in agreement with the formula $C_9H_{14}O_5$.

Assuming that two molecules of water are taken up on hydrolysis the formula of the acid would be $C_9H_{14}O_5$.

$$C_{17}H_{23}O_5N + 2H_2O = C_8H_{13}O_2N + C_9H_{14}O_5$$

The name Jacocinecic Acid has been applied to this acid.

The results from the analysis of Jacodine are in agreement with the formula $C_{18}H_{25}O_5N$, and is isomeric with Senecionine but differs from the latter in having a lower melting point and a much higher optical rotation.

Jacodine on hydrolysis also yielded a base Retronecine, $C_8H_{13}O_2N$ and an acid now called Jacodinecic Acid, which was obtained in a crystalline form but except for the equivalent has not been analysed.

In order to confirm the formulas of the above alkaloids it is necessary to have a greater quantity of the hydrolytic acidic fragments, and it is hoped to obtain these when a further supply of the

alkaloids is available.

From the optical rotations, the two alkaloids were present in the second batch of plants in about equal proportions, which was confirmed later by the isolation of the bases. In the first batch of plants collected in the early part of the season the mixture consisted of approximately 90% of Jacocine and 10% of Jacodine.

Moreover a third alkaloid is present in Senecio Jacobaea.

It was found that the mother liquors from which Jacocine and Jacodine were separated, on long standing deposited a crude residue of alkaloid which was very soluble in alcohol, and in the pure state had a very much lower melting point than the above alkaloids.

The analysis of the base corresponded to the formula $C_{17}H_{23}O_7N$, but there was not a sufficient amount of the alkaloid to confirm the formula by means of the hydrolytic products.

The name Jaconine is given to this alkaloid.

I have failed to confirm the statement of Grandval and Lajoux that Senecio Jacobaea contains the same alkaloids as Senecio vulgaris.

I have also failed to confirm the formula $C_{18}H_{23}O_5N$ of Manske's Jacobine. It should be noted, however, that the results of his analysis of the base agree better with the formula $C_{17}H_{23}O_5N$ rather than $C_{18}H_{23}O_5N$.

He probably assumed that the alkaloid should contain 18 carbon atoms similar to the known Senecio alkaloids, although in his analysis of the methiodide he gives the theoretical figurs both for $C_{17}H_{23}O_5N \cdot CH_3I$ and $C_{18}H_{23}O_5N \cdot CH_3I$, the results found being intermediate.

In the hydrolysis of the base he found Retronecine, $C_8H_{13}O_2N$, and an acid named Jaconecic Acid, to which he gives (with reserve) the formula $C_{10}H_{16}O_6$ but which obviously does not agree with the formula $C_{18}H_{23}O_5N$.

The figures of the analysis of the acid fit equally well for an acid $C_9H_{14}O_5$ which is in agreement with the hydrolysis of the base $C_{17}H_{23}O_5N$.

$$C_{17}H_{23}O_5N + 2H_2O = C_8H_{13}O_2N + C_9H_{14}O_5.$$

It must be assumed that either the alkaloid he obtained was not pure or that the species grown in Canada produces different alkaloids and for these reasons the name Jacobine has not been associated with any of the alkaloids isolated in the present research.

Senecio aquaticus although botanically very similar to Senecio Jacobaea, does not resemble the latter species in its alkaloids.

It yielded an impure form of Senecionine, $C_{18}H_{25}O_5N$, which was purified with difficluty as in the case of the alkaloid from Senecio vulgaris.

The impure base on hydrolysis gave Retronecine but the acidic fragment was a syrup which could not be crystallised and which confirmed the presence of another base.

Senecio erucifolius is a very rare plant in Scotland, and I spent much time trying to locate it in Berwickshire without much success. I ultimately found a few specimens near the village of Swinton where it was first observed in Scotland in 1827.

Later, in September, while on a visit to York, I found a few plants on the coast at Filey, and also a patch of plants on the roadside between York and Malton.

I collected 10 lbs. which yielded about 20 milligrammes of a crude base, from which I obtained a few milligrammes of the pure alkaloid.

The analysis of carbon and hydrogen was carried out and from the result the formula would appear to be $C_{18}H_{27}O_5N$. There was not sufficient

material for a nitrogen determination.

Although the melting point is near that of other known Senecio alkaloids, the alkaloid is remarkable in subliming in a high vacuum at 100°, 40° less than Senecionine.

The name Erucifoline is suggested for this alkaloid.

Group II.

The only representatives of this group investigated in the present thesis are Senecio sylvaticus and Senecio saracenicus.

The separation of the alkaloids from species of this group presented greater difficulties than those of Group I.

The crude alkaloids are obtained as dark brown coloured syrups which could not be crystallised from the usual solvents, and at first it was only by adopting Müller's method of extraction that any progress was made.

The method of purification was ultimately greatly simplified by utilising the volatility of the alkaloid, to which he does not refer.

Senecio sylvaticus was not very plentiful and the plants were collected too late in the season.

The small supply enabled me to confirm the properties of Müller's Silvasenecine without being able to isolate it.

Of Senecio saracenicus, a much larger supply was available. I collected, in July, 45 kilogrammes near Edinburgh.

The plant, although an introduction and

sometimes grown in gardens, happended to be recorded in the Flora of the Clyde Area as abundant on the banks of the Garnock, Ayrshire, and from this source a further 37 kilogrammes were obtained in August.

From this species three new bases were isolated.

From the acidulated aqueous extract of the plant a very volatile alkaloid was obtained in a crystalline form. The amount only permitted of the analysis of carbon and hydrogen being carried out and the analytical results and great volatility are compatible with the formula C_5H_9ON.

The name Saracebine has been given to this alkaloid.

From the crude base obtained from an alcohlic extract of the plant two bases were ultimately separated as syrupy liquids by fractional distillation.

The lower fraction gave a crystalline picrate and methiodide, and from the analysis of these derivatives the formula $C_8H_{13}ON$ of this new base was established, and to which the name Saracedine is applied.

This base is presumably closely related to Retronecine, $C_8H_{13}O_2N$, the basic fission product

of several Senecio alkaloids. The ready formation of a methiodide indicates that it is a tertiary base. When it is heated with zinc dust the vapours give the pine wood reaction (pyrrole ring).

The boiling point 220°/760 mm. is very near to that of Retronecanol 224°/760 mm.

It is probably unsaturated, reducing gold chloride, and has two hydrogen atoms less than Retronecanol, $C_8H_{15}ON$.

The base is optically inactive.

The higher boiling fraction yielded a crystalline aurichloride from which the formula of the base was found to be $C_{13}H_{21}ON_3$, and to which the name Saracenine is applied.

No suggestion as to its constitution is made.

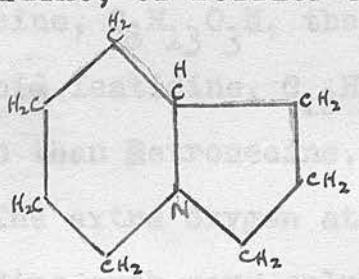
Four British species remain to be investigated, but so far material has not been available.

THE CONSTITUTION OF THE SENECIO ALKALOIDS.

It may be surmised from the work of Barger, Seshadri, Watt and Yabuta, that Retronecine, $C_8H_{13}O_2N$, the hydrolytic basic fragment from the alkaloid Retrorsine, $C_{18}H_{25}O_6N$, is a tertiary base with the nitrogen common to two rings, e.g. piperidine and pyrrolidine.

If these two rings are actually present, however, Retronecine on reduction should furnish one of the active forms of piperolidine, $C_8H_{15}N$, e.g. δ-Coniceine.

Piperolidine, of Löffler and Kaim,



the racemic form of δ-Coniceine, also termed octahydropyrrocoline by Clemo and Ramage, is isomeric with Tropane, $C_8H_{15}N$, and there is indeed a similarity between the alkaloids of Senecio and Atropa Belladonna, both being esters and both apparently mydriatic. (See Hamet and Vignes Pt.I p.14)

Nevertheless Retronecane, $C_8H_{15}N$, obtained from Retronecine, $C_8H_{13}O_2N$, via Retronecanol, $C_8H_{15}ON$,

is apparently not identical with piperolidine, the melting point of Retronecane picrate being 240°, and that of piperolidine picrate 226°. (Löffler and Kaim)

A direct comparison has not yet been made, nor has it been possible to compare Retronecine with Heliotridine, $C_8H_{13}O_2N$, the basic fission product from a somewhat similar alkaloid, Heliotrine, $C_{16}H_{27}O_5N$, which was isolated from Heliotropium lasiocarpum by Menschikoff in 1932.

From Heliotridine a base Heliotridane, $C_8H_{15}N$, was prepared, which is also isomeric with Tropane, and may be identical with Retronecane.

Isatinecine, $C_8H_{13}O_3N$, the hydrolytic base from the alkaloid Isatidine, $C_{18}H_{25}O_7N$, contains one more oxygen than Retronecine, and may be hydroxy-retronecine. The extra oxygen atom makes the alkaloid Isatidine much more soluble in water, indeed, so much so, that it was at first not recognised as an alkaloid.

It seems not unlikely that the extra oxygen atom is in the pyrrolidine ring, since the alkaloid is extraordinarily unstable to acids, yielding a substance similar to pyrrole red. (See experimental part).

Whatever the ring system in the Senecio alkaloids, it always appears to include a heterocyclic five ring capable of yielding the pyrrole reaction by distillation with zinc dust.

Retronecine, $C_8H_{13}O_2N$, is by far the most frequent basic hydrolytic product, given as is now shown by the alkaloids Senecionine, Jacocine and Jacodine, in addition to Retrorsine.

It is also indicated by the pyrrole reaction on pine wood when Jaconine, Saracedine and Saracenineare subjected to zinc dust distillation.

From the alkaloids of group I containing eighteen carbon atoms, isomeric dibasic acids of the formula $C_{10}H_{16}O_6$ have been isolated; from Senecionine the dibasic acid has only been obtained as a lactone acid $C_{10}H_{14}O_4$.

The alkaloids forming group II containing about 13 carbon atoms may perhaps yield acids of molecular weight conceivably related to Asahina's Senecionic Acid, $C_5H_8O_2$ = ββ-dimethylacrylic acid, but owing to the small yield of alkaloids, it has not yet been possible to carry out the hydrolysis in group II.

The acids obtained from the hydrolysis of alkaloids of group I appear all to have two carboxyl groups and mostly two alcoholic hydroxyl groups (in Visconecic Acid only one is present).

Retrorsine is hydrolysed to Retronecine and Retronecic Acid by taking up two molecules of water.

$$C_{18}H_{25}O_6N + 2H_2O = C_8H_{13}O_2N + C_{10}H_{16}O_6$$

One of these molecules of water breaks one ester linking, but whether the second molecule also enters into an ester linking or a lactone group is uncertain.

In the former case both active hydrogens of the Retronecine half would disappear and the two active hydrogens of Retrorsine would be in the two hydroxyl groups. In the latter case one hydroxyl would survive in the Retronecine portion and one in the acidic half, which would contain a lactone group pre-formed in the alkaloid.

The second alternative appears to be the more likely, for whilst diacetyl-Retronecine is catalytically reduced to monoacetylretronecine with loss of acetic acid, no analagous reaction takes place in a similar reduction of Retrorsine; Tetra-hydro-retrorsine, $C_{18}H_{29}O_6N$, seems to contain a

lactone group but no free carboxyl group analagous to that of the acetic acid lost in the reduction of diacetylretronecine.

Tetra-hydro-retrorsine does not have the properties of an amino acid and is not amphoteric.

A subsidiary argument to the same effect is the isolation from Senecionine of a lactone acid (Visconecic Acid).

The partial synthesis of Retrorsine was attempted in the same way as that of Atropine, by heating an equimolecular mixture of Retronecine and Retronecic Acid in a current of hydrogen chloride for seven hours at 140°.

A new base was indeed obtained in small quantity, very soluble in water and little soluble in organic solvents, which still contains one free carboxyl group.

The experiment is more likely to prove successful with the monolactone of Retronecic Acid or with Visconecic Acid.

The partial synthesis of Retrorsine is evidently more complicated than that of Atropine, since in the former case there are two hydroxyl groups in one half and two carboxyl groups in the other, whilst in the latter there is only one group

involved in either half.

A simple model experiment of the preparation of Mandelyl Retronecine should be undertaken if the alleged mydriatic action of the alkaloid is substantiated.

An attempt to identify the free hydroxyl groups in Retrorsine by the action of Grignard reagent has so far not been successful.

The following tables show the hydrolytic products previously isolated.

BASES.

Alkaloid.	Base.	M.P.		Author.
Senecifoline. $C_{18}H_{27}O_8N$.	Senecifolinine. $C_8H_{11}O_2N$.	168° (a)	-12°36'	Watt
Retrorsine. $C_{18}H_{25}O_6N$.	Retronecine. $C_8H_{13}O_2N$.	164° (a)	-	Manske.
Jacobine. $C_{18}H_{23}O_5N$.	"	164° (a)	-	Manske.
Retrorsine. $C_{18}H_{25}O_6N$.	"	121°	+50.2°	Barger etc.
Platyphylline. $C_{17}H_{25}O_5N$.	Platynecine. $C_7H_{13}O_2N$.	209° (b)	-	Orechoff.

(a) hydrochloride. (b) aurichloride.

ACIDS.

Alkaloid.	Acid.	M.P.		Author.
Senecifoline. $C_{18}H_{27}O_8N$.	Senecifolic. $C_{10}H_{16}O_6$.	198°	+28°22'	Watt.
Retrorsine. $C_{18}H_{25}O_6N$.	Retronecic. $C_{10}H_{14}O_5$.	186° (a)	-	Manske.
Jacobine. $C_{18}H_{23}O_5N$.	Jaconecic. $C_{10}H_{16}O_6$.	178°	-	Manske.
Retrorsine. $C_{18}H_{25}O_6N$.	Retronecic. $C_{10}H_{16}O_6$.	177°	-11.36°	Barger etc.
Platyphylline. $C_{17}H_{25}O_5N$.	Platynecic. $C_{10}H_{14}O_4$.	154°	+37.9°	Orechoff.

(a) Retronecic monolactone.

The following tables show the hydrolytic products isolated in this investigation.

BASES.

Alkaloid.	Base.	Formula.	M.P.	Optical rotation.
Isatidine. $C_{18}H_{25}O_7N$.	Isatinecine.	$C_8H_{13}O_3N$.	180°	+22.5°
Senecionine. $C_{18}H_{25}O_5N$.	Retronecine.	$C_8H_{13}O_2N$.	119°	+52.19°
Jacocine. $C_{17}H_{23}O_5N$.	Retronecine.	$C_8H_{13}O_2N$.	119°	+50.5°
Jacodine. $C_{18}H_{25}O_5N$.	Retronecine.	$C_8H_{13}O_2N$.	119°	

ACIDS.

Alkaloid.	Acid.	Formula.	M.P.	Optical rotation.
Isatidine. $C_{18}H_{25}O_7N$.	Isatinecic.	$C_{10}H_{16}O_6$.	148°	+88.26°
Senecionine. $C_{18}H_{25}O_5N$.	Visconecic.	$C_{10}H_{14}O_4$	147°	+34.56°
Jacocine. $C_{17}H_{23}O_5N$.	Jacocinecic.	$C_9H_{14}O_5$.?	-	-
Jacodine. $C_{18}H_{25}O_5N$.	Jacodinecic.	$C_{10}H_{14}O_5$?	136°	-

Part II

EXPERIMENTAL.

EXTRACTION.

General Process for Alkaloids of Group I

The following process was the result of a number of experiments and it was found applicable to most species of this group.

The coarsely powdered herb was well mixed with 5% of its weight of slaked lime and percolated with 95% alcohol until the percolate gave no further reaction with Mayer's reagent.

It was found that the addition of lime prevented the formation of troublesome emulsions with chloroform in later stages of the extraction.

The alcohol was recovered by distillation in vacuo, and an extract of the alkaloid containing much chlorophyll and resinous matter was obtained.

The extract was treated with a 2% solution of hydrochloric acid, filtered, and the filtrate shaken with ether to remove colouring matter.

It was then made alkaline with ammonia and the alkaloid completely extracted by shaking with successive quantities of chloroform.

The combined chloroform extracts were concentrated to a small volume and the alkaloid extracted with a 2% solution of hydrochloric acid. Non-basic material and much of the colouring matter remained in the chloroform at this stage.

The acid solution was filtered and the filtrate made alkaline with ammonia. The alkaloid was again extracted by shaking the solution with successive quantities of chloroform.

The combined chloroform extracts were washed with water to remove ammonia, and, on recovery of the solvent by distillation, a brown syrupy crystalline mass of alkaloid remained behind.

Most of the alkaloid separated out in a fairly pure state on the addition of absolute alcohol or ethyl acetate and it was further purified by recrystallisation.

In the case of Senecio venosus the lime was omitted and a troublesome emulsion was formed with chloroform which did not separate on long standing.

It was necessary to clarify the acid extract by the addition of solution of lead acetate which removed much resinous and colouring matter.

The excess of lead was precipitated from the

filtrate with dilute sulphuric acid and, on making the solution alkaline with ammonia, the alkaloid was easily extracted with chloroform.

Senecio isatideus presented further difficulties.

The dried powdered material was percolated with 95% alcohol. The percolate gave a faint reaction with Mayer's reagent but there was a copious precipitate with a solution of phospho-tungstic acid.

The alcohol was recovered by distillation in vacuo but on this occasion the residual extract contained a mass of crystals mixed with much chlorophyll and resinous matter.

It is necessary to recover the alcohol under diminished pressure. In another experiment on a small scale when the alcohol was recovered under ordinary pressure no crystals were obtained in the extract, nor did they separate from the acid solution on treatment with ether as described below.

The residual extract was treated with a 2% solution of hydrochloric acid, filtered and the filtrate shaken with ether to remove colouring matter.

The filtrate was then made alkaline with ammonia and shaken with chloroform.

On standing for a short time a distinct layer of light green coloured crystals separated in the aqueous layer and were filtered out.

The chloroform was removed, fresh chloroform added and on standing for 24 hours a further crop of crystals were obtained.

This peculiar behaviour is reminiscent of the isolation of urocanic acid from urine by Jaffe.

It would appear that the removal of some impurity by ether favours crystallisation.

The crystals were found to be the new alkaloid which is now called Isatidine.

The combined chloroform extracts were treated with 2% solution of hydrochloric acid and the acid solution was filtered. The filtrate was made alkaline with ammonia and the alkaloid again completely extracted with chloroform.

The chloroform was recovered by distillation and the residual extract was a brown varnish which was neutralised with a 1% solution of nitric acid after the method employed by Watt.

On evaporation of the solution there was no

separation of crystalline nitrate and the free base was again generated, dissolved in hot alcohol, from which it separated on cooling in prisms.

The base was identified as Retrorsine.

It was found in a subsequent experiment that the alkaloid separated out from the varnish like extract on the addition of ethyl acetate and it was easily purified by recrystallisation.

Extraction of Alkaloids of Group II.

The general process of extraction for alkaloids of Group I was also used for this group. It was found, however, that the alkaloids were partly soluble in water, so that they were not so readily extracted with chloroform. It was necessary to repeat the extraction with chloroform several times.

It was also noted that the alkaloids of this group gave a reaction with Mayer's reagent, but the precipitate was oily and did not tend to flocculate as in the case of the alkaloids of group I.

The final chloroform extract of the crude alkaloids was a dark brown coloured syrup which could not be recrystallised from the usual solvents.

The crude base thus obtained from 24 kgs. of Senecio saracenicus was ultimately treated by the method of Müller.

It was dissolved in dilute solution of sulphuric acid and the alkaloid precipitated by means of phosphotungstic acid. The phosphotungstate was collected, dried and dissolved in a 5% solution of ammonia.

The ammoniacal solution was filtered and the alkaloid extracted by shaking with successive quantities of chloroform.

The combined chloroform extracts were dried over anhydrous sodium sulphate, and on recovery of the solvent the base was obtained as a light brown coloured syrup.

Preparation of the Gold Salt.

The syrupy base was dissolved in dilute solution of hydrochloric acid and filtered.

The filtrate was treated with one drop of a 1% solution of gold chloride, the amorphous brown flakes filtered off, and the process repeated. The solution was now a bright light golden colour without turbidity.

A 10% solution of gold chloride was then added which precipitated the gold salt in light canary coloured needles.

It was found to be a new alkaloid to which the name Saracenine is applied.

It was again obtained, as described later, by the fractional distillation of the crude base.

Following up Müller's method of extraction, 1 kg. of the powdered material of Senecio saracenicus was macerated with 4 litres of hot water containing 1% of acetic acid. The mixture was put in a filter bag and pressed, and the process of extraction repeated with 1 litre of water and again pressed.

The combined aqueous extracts were filtered and the filtrate further clarified by the addition of 120 c.c. of a 20% solution of lead acetate to each litre of filtrate.

The copious precipitate was filtered out and the excessive lead was removed from the filtrate with dilute sulphuric acid, instead of hydrogen sulphide as used by Müller.

The alkaloid was then precipitated with a solution of phosphotungstic acid and extracted as described above.

From the final chloroform extract 0.75 grm. of a light brown coloured syrup was obtained.

A small portion of the crude base was distilled in a high vacuum and it was found that the alkaloid was volatile.

The remainder of the base was distilled at 10 mm. and at bath temperature 120° - 140°, a base sublimed in long, thin needles which were collected.

It was found to be a new alkaloid to which the name Saracebine has been given.

At 160° a pale yellow liquid distilled which gave a reaction with a solution of phosphotungstic acid. This base was not obtained crystalline but was again separated as described below.

A further 49 kg. were extracted by the process employed for Group I.

15 gms. of a very dark brown coloured syrup were obtained.

10 gms. of the crude syrup were distilled first at 10 mm. bath 140°, when a pale yellow liquid distilled. At 0.01 mm. bath 200°, a green dense syrup distilled over. There was much decomposition but the vapours ceased when the bath temperature reached 250°.

The distillate was again distilled and separated into two new bases -

(1) to which the name Saracedine is applied, b.p. 100° (bath 120°) 0.01 mm. Yield 0,842 gm.

(2) which was found to be Saracenine, described above, b.p. 170° (bath up to 250°) 0.01 mm. Yield 1.08 gm.

TABLE OF YIELDS.

South African Species.

Species.	Kg.	Yield. gms.	% of dried wt.	Remarks.
S. retrorsus.	75	177	0.25	Material in late seeding stage.
S. isatideus.	7	75	1.07	Isatidine.
"	3	44.5	1.29	Isatidine 1.14% Retrorsine 0.15%
S. glaberrimus.	4.8	1.3	0.027	Material in late seeding stage.
S. venosus.	0.8	0.8	0.01	

British Species.

Species.	Month collected.	Amount. Fresh. Kg.	Amount. Dried. Kg.	Yield. gms.	% of dried wt.
S. vulgaris (1)	June	38	5.5	3.3	0.06
" (2)	Octr	120	20	3.1	0.015
S. aquaticus (1)	July	19	2.5	1.0	0.04
" (2)	Sept	50	12	2.02	0.018
S. viscosus (1)	June	2.2	0.37	0.28	0.075
" (2)	July	149	27	14.9	0.055
S. Jacobaea (1)	June	45	7	2.1	0.03
" (2)	July	145	29	16.6	0.057
S. erucifolius.	Sept	5	1	-	-
S. sylvaticus.	July	14	2.5	-	-
S. saracenicus (1)	July	24	4.5	-	-
" (2)	Aug.	49	12	2.7	0.022

RETRORSINE.

Whilst this investigation was mainly concerned with British species, the following observations, additional to those recently published by Barger and co-workers, have been made on Retrorsine.

Occurrence.

Retrorsine has been found in three additional South African species.

(1) The crude alkaloid from Senecio venosus was recrystallised from ethyl acetate in prisms. M.P. 212°. Mixed melting point with Retrorsine showed no depression.

Analysis.

5.07 mg. gave 11.410 mg. CO_2 and 3.22 mg. H_2O.

mg. gave 0.111 c.c. N 763 mm/22°

$C_{18}H_{25}O_6N$ requires C = 61.5 H = 7.1 N = 4.0

found C = 61.4 H = 7.1 N = 4.1

Optical Rotation.

C = 1.68 in absolute alcohol. ℓ = 1. a = - 0.35°

$[\alpha]_D$ = - 20.8° (Retrorsine -20.51°)

(2) The crude base from Senecio glaberrimus was recrystallised from ethyl acetate in prisms. M.P. 212°. Mixed melting point with Retrorsine - no depression.

Analysis.

3.376 mg. gave 7.640 mg. CO_2 and 2.170 mg. H_2O.

4.284 mg. gave 9.665 mg. CO_2 and 2.770 mg. H_2O.

$C_{18}H_{25}O_6N$ requires C = 61.5 H = 7.1

found C = 61.53 H = 7.19
61.72 7.23.

Optical Rotation.

C = 2.08 in absolute alcohol ℓ = 1. a = - 0.40°

$[\alpha]_D$ = - 19.23° (Retrorsine - 20.51°)

(3) The second base from Senecio isatideus was recrystallised from ethyl acetate in prisms. M.P. 212°. Mixed melting point with Retrorsine - no depression.

Optical Rotation.

C = 1.9 in absolute alcohol ℓ = 1. a = - 0.37.

$[\alpha]_D$ = - 19.47° (Retrorsine - 20.51°)

Retrorsine sublimes without decomposition in a high vacuum, 0.01 mm., bath at 160° - 170°, in well former crystals.

This is indeed a property of the Senecio alkaloids.

Salts.

Retrorsine Picrolonate is precipitated at once when an aqueous solution of picrolonic acid is added to a solution of the alkaloid in dilute acetic acid.

It was recrystallised from dilute alcohol in fine hair like crystals.

M.P. It darkens at 200° and melts at 223° with decomposition.

Retrorsine Aurichloride was prepared by adding a solution of gold chloride to a solution of the alkaloid in dilute hydrochloric acid.

It was recrystallised from dilute alcohol in deep yellow coloured needles.

M.P. 190°-191°.

Tetra-hydro-retrorsine.

3 grammes of Retrorsine dissolved in 50% alcohol were reduced catalytically, and took up two molecules of hydrogen in eight hours, and as the analysis shows, without loss of oxygen.

The solution was filtered and evaporated in vacuo, when a syrupy residue was obtained, which at first could not be crystallised.

It was extremely soluble in methyl alcohol, ethyl alcohol and readily soluble in water. It was practically insoluble in ether and ethyl acetate.

It was ultimately crystallised from ethyl acetate by evaporation at room temperature in clusters of fine needles.

M.P. 94°

Analysis.

3.875 mg. dried in a high vacuum - loss of weight 0.385 mg.

3.490 mg. gave 7.880 mg. CO_2 and 2.575 mg. H_2O.

$C_{18}H_{29}O_6N \cdot 2H_2O$ requires $2H_2O$ = 9.2%

found $2H_2O$ = 9.9%

$C_{18}H_{29}O_6N$ requires C = 60.85 H = 8.22

found C = 61.58 H = 8.25

Optical Rotation.

c = 1.83 in absolute alcohol. l = 1. α = -0.71

$$[\alpha]_D^{16^\circ} = -38.79^\circ$$

Unsaturated Lactone from Retronecic Acid.

On hydrolysing Retrorsine it was found that in addition to Retronecic Acid, which is sparingly soluble in ether, a portion was obtained which was much more soluble in ether and remained behind on evaporation of the solvent as a dark brown coloured syrup, which became partly crystalline on standing.

It was distilled at 10mm., bath up to 300°, when the acid appeared to boil and give off vapours, due to decomposition by loss of water.

The distillate was in part neutral and was separated by shaking with solution of sodium carbonate and ether.

The ether extract was dried over anhydrous sodium sulphate, and on evaporation of the ether a light yellow coloured syrup was obtained.

It distilled at 120°-130°/15 mm., and the distillate was a mobile colourless liquid.

Analysis.

3.770 mg. gave 9.790 mg. CO_2 and 2.840 mg. H_2O.

2.585 mg. gave 6.735 mg. CO_2 and 1.960 mg. H_2O.

$C_9H_{12}O_2$ requires C = 71.05 H = 7.9

found C = 70.82 H = 8.43
71.06 8.48

Equivalent calculated 152 - found 145.

Properties.

The lactone developed a deep red colour on the addition of strong solution of potassium hydroxide.

It gave no coloration with ferric chloride, but an insoluble iron salt.

It does not reduce ammoniacal silver nitrate, but gives a silver salt.

ISATIDINE.

The crude alkaloid was recrystallised from 90% alcohol and separated in long prisms.

It dissolves readily in cold methyl alcohol, in hot ethyl alcohol and in hot water. It is almost insoluble in chloroform, ethyl acetate, acetone and ether.

M.P. The melting point is very indefinite about 144° - 145° with decomposition.

Analysis.

5.417 mg. dried at 100° in a high vacuum lost 0.518 mg.

4.894 mg. gave 10.615 mg. CO_2 and 3.010 mg. H_2O.

6.884 mg. gave 0.233 c.c. N at 750mm/22°

7.722 mg. gave 0.261 c.c. N at 750mm/21°

$C_{18}H_{25}O_7N \cdot 2H_2O$ requires $2H_2O = 8.93$

found $2H_2O = 9.55$

$C_{18}H_{25}O_7N$ requires C = 58.85 H = 6.81 N = 3.81

found C = 59.15 H = 6.88 N = 3.87

Optical Rotation.

c = 1.16 in absolute alcohol l = 1 a = -0.37°

$[\alpha]_D = -31.9^{\circ}$

Properties.

Isatidine gives no precipitate with Mayer's reagent, but it is precipitated by Dragendorff's

reagent up to 1 in 15000 in acid solution, and by solution of phosphotungstic acid up to 1 in 10000.

The phosphotungstate crystallises in plates.

It gives a soluble aurichloride and a soluble picrate neither of which could be crystallised.

A characteristic property of Isatidine is its instability to acids. A solution in dilute hydrochloric acid gives a black residue on evaporation on the water bath.

It at once darkens on boiling with acetic anhydride, and its solution in acetic anhydride in the cold gives after some time a dark reddish or purplish precipitate insoluble in organic solvents, and is probably a polymeride analagous to pyrrole red.

Isatidine darkens and decomposes almost at once at 140° in a high vacuum.

Hydrolysis.

The separation of the two hydrolytic fission products of Senecio alkaloids, both readily soluble in water, is greatly facilitated by the use of Plaster of Paris, as originally worked out for Retrorsine by Yabuta, and was employed throughout the present investigation.

This method is distinctly superior to that

used by Watt, Manske, Menschikoff and Orechoff, who with some difficulty, had to separate the basic product as the hydrochloride or aurichloride from inorganic salts.

In the case of Isatidine the method required slight modification as indicated below.

1 gramme was dissolved in 20 c.c. of a 10% alcoholic solution of potassium hydroxide and allowed to stand for three hours at room temperature.

It was then heated under a reflux condenser for one hour. The solution darkened in colour very slightly, and when cold was made acid to congo red with hydrochloric acid and evaporated in vacuo. Decomposition took place and the solution became dark red in colour.

It was necessary to adopt the following modification.

5 grammes were dissolved in 100 c.c. of normal solution of barium hydroxide and boiled under a reflux condenser for three hours.

Sulphuric acid was then added until the solution was acid to phenolphthalein and the precipitated barium sulphate filtered out and washed thoroughly with water.

The filtrate and the washings were evaporated

to dryness and the residue extracted with absolute alcohol, which dissolved the basic fragment, Isatinecine, but did not dissolve the barium salt of Isatinecic Acid.

The alcoholic solution was concentrated and allowed to stand, when a few large crystals separated (one crystal weighed 80 milligrammes) and a further crop was obtained on the careful addition of acetone.

Yield. - 1.49 gms.

The barium salt of the acid was dissolved in water and the solution was made acid to congo red with dilute sulphuric acid. The precipitated barium sulphate was filtered out and the solution of the free acid was evaporated to dryness.

The residue was mixed with Plaster of Paris and continuously extracted in a soxhlet apparatus with anhydrous ether. Crystals of the acid separated in the receiver during the extraction.

Yield. - 3.06 gms.

ISATINECINE.

The crude base was recrystallised from absolute alcohol and acetone in colourless stout prisms.

Solubility.

It is very soluble in methyl alcohol and ethyl alcohol, moderately soluble in water, very sparingly soluble in acetone and ether, and almost insoluble in chloroform.

M.P. At 180° it turns yellow in colour and melts with decomposition at 210°.

Analysis.

4.210 mg. gave 8.610 mg. CO_2 and 2.885 mg. H_2O.

3.900 mg. gave 7.945 mg. CO_2 and 2.620 mg. H_2O.

$C_8H_{13}O_3N$ requires C = 56.14 H = 7.6

found C = 55.78 H = 7.59
55.56 7.52

Optical Rotation.

C = 5.20 in water. l = 1. a = +1.17°

$[\alpha]_D$ = +22.5°

Properties.

Isatinecine shows the same sensitiveness to acids, and on evaporation with dilute hydrochloric acid on the water bath gives a violet black residue.

It is not precipitated by Mayer's reagent.

The phosphotungstate crystallises in needles,

and is soluble in excess of the reagent.

An aqueous solution is only very slightly alkaline to litmus and does not reduce Fehling's solution.

Isatinecine gives no reaction with diazomethane.

Benzoylation of Isatinecine by Schotten-Baumann Method.

Isatinecine was dissolved in a solution of sodium hydroxide and after the addition of each drop of benzoyl chloride, the mixture was shaken at once.

A semi-solid precipitate was ultimately separated and washed with sodium hydroxide solution and then with water by decantation.

It was dissolved in much ether, washed first with sodium carbonate solution, and then with water, and dried over potassium carbonate.

The ether was evaporated by an air blast , when crystals separated.

It could not be crystallised from chloroform or alcohol, but at first only from ether at room temperature.

The crystals were ultimately recrystallised from petroleum ether (b.p. 100°) in long needles. M.P. 108° blackening slightly at higher temperature.

Analysis.

3.821 mg. dried in a high vacuum - no loss of wt.

3.821 mg. gave 10.210 mg. CO_2 and 1.815 mg. H_2O.

3.50 mg. gave 9.460 mg. CO_2 and 1.670 mg. H_2O.

2.425 mg. gave 0.086 c.c. N 757 MM/17°

3.971 mg. gave 0.137 c.c. N 757 mm/17.5°

$C_{22}H_{19}O_4N$ requires C = 73.13 H = 5.36 N = 3.9

found C = 72.9 H = 5.3 N = 4.2
72.9 5.3 4.0

The composition corresponds to a Dibenzoyl-anhydro-isatinecine, $C_8H_9O_2N(C_6H_5CO)_2$

Properties.

It is a neutral substance, insoluble in solution of sodium hydroxide or hydrochloric acid.

When it is heated with strong hydrochloric acid, it turns red and black particles separate.

The pure benzoyl derivative is destroyed by evaporating a chloroform solution on the water bath.

Benzoylation with pyridine and benzoyl chloride was unsuccessful.

ISATINECIC ACID.

The crude base was recrystallised from ethyl acetate and separated in aggregates of long narrow prisms.

Solubility.

It is soluble in water, alcohol, acetone and chloroform, but sparingly soluble in ether and ethyl acetate.

M.P. 148°

Analysis.

4.810 mg. gave 9.150 mg. CO_2 and 2.970 mg. H_2O.

$C_{10}H_{16}O_6$ requires C = 51.72 H = 6.9

found C = 51.90 H = 6.9

Equivalent calculated 116 - by titration 115.

Optical Rotation.

c = 2.3 in water. ℓ = 1. a = +2.03°

$[\alpha]_D$ = +88.26°

Properties.

A solution of Isatinecic Acid reduces an alkaline solution of potassium permanganate in the cold.

The normal potassium salt is insoluble in methyl alcohol and absolute alcohol.

Di-methyl Ester of Isatinecic Acid.

The ester was prepared by adding a saturated

solution of diazomethane in ether to a solution of the acid in methyl alcohol.

On evaporation of the solvent the ester was obtained as a dense syrupy liquid.

B.P. about 200°/1 mm.

Di-p-phenylphenylacyl Ester of Isatinecic Acid.

1 millimol of the acid was dissolved in 0.5 c.c. of water, neutralised with sodium carbonate and then made slightly acid with Isatinecic Acid.

1 c.c. of absolute alcohol and 1 millimol of p-phenylphenylacyl bromide were added and the mixture was heated under a reflux condenser for one hour.

The ester crystallised out on cooling the solution and was recrystallised from absolute alcohol in fine needles.

M.P. 152°

SENECIONINE.

The crude alkaloid was recrystallised from absolute alcohol and separated in rhombic plates.

Solubility.

It is very soluble in chloroform, from which it can be recrystallised by the addition of petroleum ether.

It is sparingly soluble in alcohol and ethyl acetate, and almost insoluble in water, ether and acetone.

M.P. 232°

The melting point and solubility in absolute alcohol of the alkaloids obtained from the various species was determined with the following results.

Species.	Solubility. w/w 15°	M.P.
Ex Senecio aquaticus.	1 in 225	224°
Ex Senecio vulgaris (1)	1 in 280	220°
" " (2)	1 in 340	232°
x Ex Senecio Viscosus.	1 in 345	232°

x Pure Senecionine.

Analysis.

Alkaloid ex Senecio aquaticus. 1st batch.

5.439 mg. gave 12.765 mg. CO_2 and 3.530 mg. H_2O.

3.211 mg. gave 0.122 c.c. N 758 mm/25°

$C_{18}H_{25}O_5N$ requires C = 64.47 H = 7.46 N = 4.18

found C = 64.41 H = 7.21 N = 4.34

Alkaloid ex Senecio aquaticus. 2nd batch.
5.072 mg. dried in a high vacuum at 100°- loss in wt. 0.222 mg.
4.850 mg. gave 11.355 mg. CO_2 and 3.080 mg. H_2O.

$C_{18}H_{25}O_5N$ requires C = 64.47 H = 7.46 H_2O = 4.88%

found C = 63.85 H = 7.11 H_2O = 4.38%

Alkaloid ex Senecio vulgaris. 1st batch.
1st. fraction.

$C_{18}H_{25}O_5N$ requires C = 64.47 H = 7.46 N = 4.18

found C = 64.27 H = 7.08 N = 4.07
64.37 7.22
64.17 7.18

2nd. fraction.(further purified by recrystallisation)

5.097 mg. gave 11.885 mg. CO_2 and 3.320 mg. H_2O.

$C_{18}H_{25}O_5N$ requires C = 64.47 H = 7.46

found C = 63.81 H = 7.31

Alkaloid ex Senecio viscosus.

$C_{18}H_{25}O_5N$ requires C = 64.47 H = 7.46 N = 4.18

found C = 64.36 H = 7.47 N = 4.18

Optical Rotations.

Alkaloid.		c in $CHCl_3$	ℓ	α	$[\alpha]_D$
Ex Senecio aquaticus	(1)	1.705	1	-1.20°	-70.38°
" "	(2)	4.565	2	-6.40°	-70.08°
Ex Senecio vulgaris.	(1)	2.15	1	-1.74°	-80.93°
x " "	(2)	4.911	2	-5.46°	-55.59°
x Ex Senecio viscosus	(1)	1.63	1	-0.89°	-54.6°
x " "	(2)	4.607	2	-5.12°	-55.56°

x Pure Senecionine.

Senecionine sublimes in a high vacuum 0.01 mm. bath at 140°, without decomposition, in well formed crystals.

Salts.

Senecionine Picrate was precipitated at once on the addition of an aqueous solution of picric acid to a solution of the alkaloid in dilute acetic acid.

It was recrystallised from dilute alcohol in fine needles.

M.P. 191° (ex alkaloid S. vulgaris 1st batch 184°)
(ex alkaloid S. aquaticus 186°)

Senecionine Methiodide was quickly deposited when methyl iodide was added to a solution of the alkaloid in chloroform.

It was recrystallised from absolute alcohol, in which it is sparingly soluble, in colourless prisms.

M.P. 249° darkening at 230°.
(ex alkaloid S. vulgaris 1st batch 238°)
(ex alkaloid S. aquaticus 241°)

Senecionine Picrolonate was precipitated on the addition of an aqueous solution of picrolonic acid to a solution of the alkaloid in alcohol.

It was recrystallised from dilute alcohol in fine hair like crystals.

M.P. 183°

Senecionine Aurichloride was precipitated on the addition of a solution of gold chloride to a solution of the alkaloid in hydrochloric acid.

It was recrystallised from dilute alcohol in deep yellow coloured needles.

M.P. 186°

Senecionine Nitrate was prepared by dissolving the alkaloid in the calculated quantity of 0.1 normal solution of nitric acid, evaporating the solution to a small volume on the water bath and finally in a vacuous desiccator.

It crystallised from water in prisms, and was recrystallised from absolute alcohol in small rhombic plates.

Senecionine nitrate is sparingly soluble in absolute alcohol, but very soluble in water.

M.P. 214°.

Analysis.

4.750 mg. gave 9.480 mg. CO_2 and 2.780 mg. H_2O .

$C_{18}H_{25}O_5N \cdot HNO_3$ requires C = 54.27 H = 6.53

found C = 54.43 H = 6.51

Optical Rotation.

c = 1.14 in water. $\ell = 1.$ $\alpha = -0.39°$

$[\alpha]_D^{16°} = -34.21°$

Hydrolysis.

1 gramme was hydrolysed by boiling with 20 c.c. normal solution of sodium hydroxide for two hours.

BASE.

The crude base was recrystallised from methyl alcohol and acetone (one crystal weighed 170 milligrammes).

M.P. 119°. Mixed melting point with pure Retronecine showed no depression.

Optical Rotation.

c = 2.04 in absolute alcohol. $\ell = 1$. $\alpha = +1.08^{\circ}$

$[\alpha]_D = +52.19^{\circ}$ (Retronecine = $+50.81^{\circ}$)

The base is Retronecine, $C_8H_{13}O_2N$.

VISCONECIC ACID.

The acid was obatined as a syrupy, partly crystalline mass, which was further crystallised on dissolving in ethyl acetate and allowing the solvent to evaporate.

The acid distilled at 0.01 mm., bath at 180°, almost completely as a colourless liquid which solidified.

It was dissolved in boiling chloroform and concentrated greatly. Petroleum ether added and again concentrated, when it slowly crystallised to

a mass of needles in aggregates.

The crystals were filtered off and washed with a mixture of ether and petroleum ether.

Solubility.

Visconecic Acid is very soluble in water, alcohol, ether, acetone, chloroform and ethyl acetate, but almost insoluble in petroleum ether.

M.P. 147°

Analysis.

3.647 mg. gave 8.105 mg. CO_2 and 2.445 mg. H_2O.

$C_{10}H_{14}O_4$ requires C = 60.60 H = 7.12

found C = 60.61 H = 7.50

Equivalent calculated 198 - by titration 199.

Back titration showed the presence of a lactone group.

Optical Rotation.

c = 0.81 in absolute alcohol. $\ell = 1$. $[\alpha] = +0.28^\circ$

$[\alpha]_D^{16^\circ} = +34.56^\circ$

THE ALKALOIDS OF SENECIO JACOBAEA.

The crude base obtained from the first batch of plants, collected in June, was recrystallised from absolute alcohol, and separated in glistening nacreous rhombic plates.

Solubility.

The alkaloid was very soluble in chloroform, sparingly soluble in ether, moderately soluble in alcohol and ethyl acetate, and insoluble in water.

M.P. 211°

Analysis.

$C_{18}H_{23}O_5N$	requires	C = 64.86	H = 6.90	N = 4.20
	found	C = 61.94	H = 7.36	N = 4.03
		61.63	7.05	
		61.87	7.36	

Optical Rotation.

c = 1.405 in chloroform. $l = 1$. $\alpha = -0.88°$

$$[\alpha]_D = -62.63°$$

The crude base obtained from the second batch of plants, collected in July, was recrystallised from absolute alcohol, and again separated in the characteristic nacreous rhombic plates.

The solubility of the alkaloid in absolute alcohol at 15° was found to be 1 in 110 w/w.

The various fractions obtained on the

recrystallisation from 95% alcohol were collected and tested for their optical activity with the following results.

No.	c in $CHCl_3$	ℓ	α	$[\alpha]_D^{17°}$	M.P.
(1)	4.889	2	-8.25°	-84.2°	211°
(2)	4.923	2	-8.13°	-82.6°	210°
(3)	2.437	2	-3.85°	-79°	210°
(4)	2.269	2	-3.65°	-80.4°	210°
(5)	4.926	2	-9.15°	-92.28°	212°
(6)	2.442	2	-4.60°	-94.18°	212°

Analysis. (Fraction No. 5)

4.640 mg. dried in a high vacuum at 100°- loss of wt. 0.437 mg.

4.203 mg. gave 9.930 mg. CO_2 and 2.580 mg. H_2O.

$C_{18}H_{23}O_5N \cdot 2H_2O$ requires $2H_2O = 9.7$

found $2H_2O = 9.42$

$C_{18}H_{23}O_5N$ requires C = 64.86 H = 6.90

found C = 64.45 H = 6.87

The great variation in the optical rotations and the not quite concordant analytical results led to the suspicion that more than one alkaloid was present in the plant.

With a view to the separation, 1 gramme of the alkaloid was dissolved in the approximate amount of 0.1 normal solution of nitric acid to form the nitrates.

The solution was evaporated to a small volume on the water bath and finally in a vacuous desiccator.

On crystallisation from absolute alcohol the nitrates were found to differ much more in solubility than the bases themselves.

It was ultimately found, however, that the free bases can be separated by fractional crystallisation from ethyl acetate.

The first fraction of crystals separated out in silvery nacreous flakes.

They were collected, dried and the yield was 0.5 grm.

M.P. 226° $[\alpha]_D^{16°}$ -34.73°

The alcohol solution was concentrated and a further supply of crystals in small rhombic plates was obtained.

Yield 0.45 grm.

M.P. 214° $[\alpha]_D^{16°}$ -75.63°

From the nitrates the bases were regenerated and found to be quite distinct; to the base from the less soluble nitrate the name Jacocine was applied and to that from the more soluble nitrate the name Jacodine.

For reasons already explained it seems desirable not to apply the name Jacobine to either.

JACOCINE.

The base regenerated from the less soluble nitrate was recrystallised from ethyl acetate in rhombic plates.

It is moderately soluble in alcohol, very soluble in chloroform, and about twice as soluble in ethyl acetate as Jacodine. It is almost insoluble in water.

M.P. 210°

Analysis.

4.926 mg. dried at room temp. in a high vacuum - no loss of weight.

4.926 mg. gave 11.215 mg. CO_2 and 3.060 mg. H_2O.

$C_{17}H_{23}O_5N$ requires C = 63.55 H = 7.16 N = 4.36

$C_{18}H_{23}O_6N$ requires C = 61.89 H = 6.59 N = 4.01

found C = 62.09 H = 6.90 N = 4.12

Optical Rotation.

c = 1.38 in chloroform. l = 1. α = -0.78°.

$$[\alpha]_D^{16^\circ} = -56.52^\circ$$

Jacocine sublimes without decomposition in a high vacuum, 0.01 mm. bath at 150°.

It is rather less volatile than Jacodine and did not give well formed crystals.

Jacocine Picrate. was prepared by adding an aqueous solution of picrate acid to a solution of the nitrate.

It was recrystallised from dilute alcohol in feathery crystals.

Jacocine picrate is much more soluble in water than Jacodine picrate.

M.P. 180°.

Jacocine Nitrate, prepared as previously described, was recrystallised from 90% alcohol in glistening nacreous flakes.

It is less soluble in water and absolute alcohol than Jacodine Nitrate.

M.P. 227°

Analysis.

4.895 mg. dried in a high vacuum at 100° lost 0.200 mg.

4.695 mg. gave 9.170 mg. CO_2 and 2.630 mg. H_2O.

$C_{17}H_{23}O_5N \cdot HNO_3 \cdot H_2O$ requires $H_2O = 4.4$

found $H_2O = 4.08$

$C_{17}H_{23}O_5N \cdot HNO_3$ requires C = 53.13 H = 6.25

found C = 53.27 H = 6.22

Optical Rotation.

c = 1.37 in water. $l = 1$. $\alpha = -0.52°$

$[\alpha]_D^{16°} = -37.94°$

Hydrolysis.

0.5 grm. was boiled with 10 c.c. of alcohol and 10 c.c. normal solution of sodium hydroxide for two hours.

BASE.

On evaporation of the chloroform the base was obtained as a light yellow coloured syrup which became solid on standing.

It was recrystallised from acetone in clusters of small prisms. Yield 0.170 grm. M.P. 119°, Mixed melting point with Retronecine - no depression.

Optical Rotation.

c = 0.099 in absolute alcohol. $l = 1$. $\alpha = +0.50^{\circ}$

$[\alpha]_D^{16^{\circ}} = +50.5^{\circ}$ (Retronecine = $+50.81^{\circ}$)

The base is Retronecine, $C_8H_{13}O_2N$.

JACOCINECIC ACID.

The acid was obtained as a syrup which became partly crystalline on long standing in a vacuous desiccator. It has also been obtained crystalline from a very concentrated solution in chloroform in pyramidal shaped crystals.

So far it has not been analysed, but a plated specimen of an acid from the hydrolysis of the mixed alkaloids gave the following results.

$C_9H_{14}O_5$ requires C = 54.45 H = 6.94

found C = 54.17 H = 6.90

An acid of the formula $C_9H_{14}O_5$ corresponds to the acid from the hydrolysis of the base $C_{17}H_{23}O_5N$.

Jacocinecic Acid is very soluble in water, alcohol, chloroform, acetone and ether. It is almost insoluble in petroleum ether.

It distils in a high vacuum 0.01 mm. bath at 180°, yielding a light yellow coloured syrup which crystallised very slowly on long standing in a desiccator.

JACODINE.

The base regenerated from the more soluble nitrate was recrystallised from ethyl acetate in long flat plates pointed at both ends.

It is more soluble in alcohol but approximately only half as soluble in ethyl acetate as Jacocine.

It is sparingly soluble in ether and almost insoluble in water.

M.P. 217°

Analysis.

4.794 mg. dried at room temp. in a high vacuum - no loss of weight.
4.794 mg. gave 11.295 mg. CO_2 and 3.100 mg. H_2O.

$C_{18}H_{25}O_5N$ requires C = 64.41 H = 7.21 N = 4.34

found C = 64.26 H = 7.18 N = 4.34

Optical Rotation.

c = 1.35 in chloroform. $\ell = 1$. $\alpha = -1.48°$

$$[\alpha]_D^{16°} = -109.63°$$

Jacodine sublimes without decomposition in a high vacuum 0.01 mm., bath at 140°, in clusters of fine needles.

Jacodine Picrate was prepared from a solution of the nitrtate by the addition of an aqueous solution of picric acid.

It was recrystallised from dilute alcohol in fine needles.

Jacodine Picrate is very little soluble in cold water.

M.P. 171°.

Jacodine Nitrate.

It was recrystallised from absolute alcohol in small rhombic plates.

It is much more soluble in alcohol and in water than Jacocine Nitrate, and does not have the same nacreous appearance.

M.P. 215°

Optical Rotation.

c = 1.33 in water. $l = 1.$ $\alpha = -1.03°$

$[\alpha]_D^{16°} = -77.44°$

Hydrolysis.

0.4 grm. of the alkaloid was hydrolysed.

BASE.

The base was obtained as a syrup which solidified but did not crystallise when dissolved in acetone.

It was distilled in a high vacuum 0.01 mm./180° as a greenish fluorescent gum which crystallised from acetone in large crystals.

M.P. 119°. Mixed melting point with Retronecine -

showed no depression.

The base is Retronecine, $C_8H_{13}O_2N$.

JACODINECIC ACID.

The acid was obtained as a syrup which did not crystallise readily from ether and petroleum ether.

It was ultimately obtained crystalline from a concentrated solution in chloroform, being deposited in sphaero-crystals or groups of needles.

Jacodinecic Acid is very soluble in water, alcohol, chloroform and ether.

M.P. 136°-137°

Equivalent by titration = 116.

So far this acid has not been analysed.

JACONINE.

The crude base which separated from the mother liquors of Jacocine and Jacodine was first crystallised from alcohol in prisms, and finally from ethyl acetate in aggregates of prisms.

Jaconine is very soluble in alcohol and chloroform and moderately soluble in ethyl acetate.

M.P. 146°

Analysis.

(1) Substance air dried.

3.385 m.g. gave 6.755 mg. CO_2 and 2.120 mg. H_2O.

2.798 mg. gave 0.287 c.c. N 20°/747 mm.

$C_{17}H_{23}O_7N \cdot H_2O$ requires C = 54.99 H = 6.74 N = 3.77

found C = 54.42 H = 6.96 N = 3.56

(2) 5.430 mg. dried at room temp. 50° lost 0.246 mg.

5.169 mg. gave 10.770 mg. CO_2 and 2.990 mg. H_2O.

$C_{17}H_{23}O_7N \cdot H_2O$ requires H_2O = 4.87

found H_2O = 4.53

$C_{17}H_{23}O_7N$ requires C = 57.78 H = 6.52

found C = 56.83 H = 6.43

Optical Rotation.

c = 0.93 in chloroform. $l = 1$. $[\alpha] = -0.43°$

$[\alpha]_D^{16°} = -46.23°$

Properties.

The crude base was distilled in a high vacuum 0.01 mm., bath at 180°, when a green fluorescent liquid was obtained which set to a glassy solid and which crystallised in flat prisms on heating the tube on a water bath.

Jaconine gives a distinct pyrrole reaction on pine wood when distilled with zinc dust.

ERUCIFOLINE.

The crude alkaloid was recrystallised from absolute alcohol and separated in flat plates pointed at both ends.

4 milligrammes were obtained.

M.P. 222°

Analysis.

1.850 mg. dried at 100° in a high vacuum 0.850 mg. sublimed.

1.021 mg. gave 2.410 mg. CO_2 and 0.750 mg. H_2O.

$C_{18}H_{27}O_5N$ requires C = 64.10 H = 8.01

found C = 64.63 H = 8.19

SARACEBINE.

The crude base was obtained in a pure condition by distilling it in a vacuum 10 mm., bath below 100°, when it sublimed in fine needles.

4 milligrammes were obtained.

The base gives a reaction with solution of phosphotungstic acid.

M.P. 117°-118°

Analysis.

2.580 mg. gave 5.800 mg. CO_2 and 2.110 mg. H_2O.

C_5H_9ON requires C = 60.60 H = 9.09

found C = 61.27 H = 9.08

SARACEDINE.

The pure base is a light yellow coloured mobile liquid.

It is very soluble in chloroform and alcohol, and partly soluble in water.

B.P. 100°/0.1 mm. 220°/760 mm.

Properties.

A solution of the base in dilute hydrochloric acid reduces a solution of gold chloride at once.

It gives a distinct pyrrole reaction on pine wood when distilled with zinc dust.

The phosphotungstate is less soluble in hot water than the phosphotungstate of Saracenine.

The base is optically inactive.

Salts.

Saracedine Methiodide.

It was prepared by heating a solution of the base in methyl alcohol with methyl iodide.

It was recrystallised from methyl alcohol in colourless prisms.

Saracedine Methiodide is only slightly soluble in absolute alcohol, but more soluble in 90% alcohol and methyl alcohol.

M.P. 204°

Analysis.

4.777 mg. gave 6.745 mg. CO_2 and 2.340 mg. H_2O.

$C_8H_{13}ON \cdot CH_3I$ requires C = 38.43 H = 5.69

found C = 38.51 H = 5.44

Saracedine Picrate.

It was prepared by the addition of an aqueous solution of picric acid to a solution of the base in dilute acetic acid.

It was recrystallised from dilute alcohol in long hair like needles.

Saracedine Picrate is also slightly soluble in absolute alcohol but very soluble in 90% alcohol.

M.P. 269°

Analysis.

2.644 mg. gave 0.341 c.c. N 23°/767 mm.

$C_8H_{13}ON \cdot C_6H_3O_7N_3$ requires N = 15.22

found N = 15.01

SARACENINE.

The pure base is a dense, yellow coloured liquid.

It is very soluble in chloroform and alcohol, and slightly soluble in water.

B.P. 170°/0.1 mm.

Optical Rotation.

c = 1.59 in chloroform. $l = 1$. $\alpha = -0.36$

$$[\alpha]_D^{16^\circ} = -22.64^\circ$$

Properties.

The base gives a distinct pyrrole reaction on pine wood when distilled with zinc dust.

The phosphotungstate is more soluble in hot water than Saracedine phosphotungstate.

The picrate is precipitated in cold water but is soluble in hot water, from which it separates in an oily condition, as also does the flavianate and picrolonate. The iodide is very soluble in cold water.

Salts.

Saracenine Aurichloride.

It was precipitated in a crystalline form on the addition of a solution of gold chloride to a solution of the base in dilute hydrochloric acid.

It was recrystallised from dilute alcohol in long fine needles.

M.P. 180°

Analysis.

5.232 mg. dried at room temp. in a high vacuum - no loss of weight.
2.912 mg. gave 2.880 mg. CO_2 1.050 mg. H_2O 1.000 mg. Au.
3.129 mg. gave 0.186 c.c. N 23°/762 mm.

$C_{13}H_{22}ON_3Cl_4Au$ requires	C = 27.13	found C = 26.98
	H = 3.82	H = 4.01
	N = 7.30	N = 6.87
	Au = 34.26	Au = 34.34

Saracenine Hydrochloride.

The hydrochloride was prepared from the aurichloride after the method of Dudley.

The aurichloride was dissolved in hot water and shaken with twice its weight of molecular silver. The solution was filtered and the filtrate evaporated to dryness in vacuo.

The residue was dissolved in hot acetone and much ethyl acetate, filtered and concentrated greatly. It was then precipitated with dry ether in whetstone shaped glistening crystals, which were filtered off and washed with acetone and ether.

It is extremely soluble in water, alcohol and acetone, and moderately soluble in ethyl acetate.

M.P. 155°

Analysis.

5.115 mg. gave 10.525 mg. CO_2 and 3.290 mg. H_2O.

2.669 mg. gave 1.320 mg. AgCl.

$C_{13}H_{21}ON_3 \cdot HCl$ requires C = 57.56 H = 8.1 Cl = 12.9

found C = 56.25 H = 7.21 Cl = 12.1

From the above results it would appear that the salt was not quite pure.

SUMMARY.

A review is given, as far as possible complete, of the literature on the pharmacological action and chemistry of the Senecio species.

The following new alkaloids have been isolated and characterised:-

ISATIDINE.	$C_{18}H_{25}O_7N$.
JACOCINE.	$C_{17}H_{23}O_5N$?
JACODINE.	$C_{18}H_{25}O_5N$.
JACONINE.	$C_{17}H_{23}O_7N$.
ERUCIFOLINE.	$C_{18}H_{27}O_5N$.?
SARACEBINE.	C_5H_9ON.?
SARACEDINE.	$C_8H_{13}ON$.
SARACENINE.	$C_{13}H_{21}ON_3$.

The alkaloid Isatidine has been shown to yield a new base ISATINECINE, $C_8H_{13}O_3N$, and a new acid, ISATINECIC ACID, $C_{10}H_{16}O_6$.

Like Retrorsine, Senecionine of Grandval and Lajoux, Jacocine and Jacodine, have been shown to yield Retronecine, $C_8H_{13}O_2N$, and the following new acidic moieties have been isolated.

VISCONECIC ACID. $C_{10}H_{14}O_4$.

JACOCINECIC ACID. $C_9H_{14}O_5$.?

JACODINECIC ACID. ---

The presence of Retrorsine in three other species, Senecio isatideus, Senecio glaberrimus and Senecio venosus has been established, as well as Senecionine in Senecio aquaticus and Senecio viscosus.

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